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HOT TOPIC

# Efficacy and Safety of Terbutaline vs. Epinephrine for Treating Pediatric Asthma in Emergency: A Systematic Review of Randomized Controlled Trials

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## Abstract

**Background** Asthma is a prevalent inflammatory airway condition characterized by reversible airflow obstruction. It poses significant health risks, especially during acute exacerbations, which can be potentially fatal if untreated. This study aims to review the safety and efficacy of terbutaline in comparison to epinephrine in treating acute pediatric asthma exacerbations in emergency settings.

**Methods** This systematic review was conducted following the PRISMA guidelines. A comprehensive literature search was performed across PubMed, MEDLINE, EMBASE, and the Cochrane Library up to December 2023. We included randomized controlled trials (RCTs) comparing the safety and efficacy of terbutaline to epinephrine in asthma exacerbation in Children aged 21 years and below in the ED. Outcomes assessed for efficacy were Forced Expiratory Volume in one second (FEV1), Forced Vital Capacity (FVC), and Peak Expiratory Flow Rate (PEF). For safety, outcomes included incidence of adverse events including Tachycardia, arrhythmias, and blood pressure changes.

**Results** Ten randomized controlled trials (RCTs) involving 510 children were included. The studies showed that both terbutaline and epinephrine significantly improved respiratory parameters, with no significant difference in adverse events. Terbutaline showed an advantage in FEV1 and FVC. Cardiovascular effects were more favorable with terbutaline, with lower increases in heart rate and blood pressure.

**Conclusions** Terbutaline and epinephrine are effective and safe for treating acute pediatric asthma exacerbations. Terbutaline's slightly better efficacy in certain respiratory parameters and favorable cardiovascular profile suggest it may be preferable in specific clinical scenarios. Further research is warranted to confirm these findings and optimize treatment protocols. PROSPERO registration (CRD42023485496).

**Keywords** Pediatric asthma · Terbutaline · Epinephrine · Systematic review · Respiratory parameters · Adverse events

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**Abbreviations**

| | |
|---|---|
| FEV1 | Forced expiratory volume in one second |
| FVC | Forced vital capacity |
| PEF | Peak expiratory flow rate |
| Bpm | Beats per minute bpm |
| SBP | Systolic blood pressure |
| DBP | Diastolic blood pressure |

## Background

Asthma stands as a prevalent inflammatory airway condition characterized by reversible airflow obstruction, with acute exacerbations posing potential fatality risks if left untreated. Its prevalence is notably high among children, affecting approximately 7.1 million individuals under the age of 18 in the United States alone [1]. Moreover, its global burden is significant, with an estimated 300 million individuals worldwide afflicted by this chronic ailment. Alarmingly, this burden is expected to escalate, potentially afflicting an additional 100 million people by 2025, primarily due to escalating urbanization and consequent increases in atopic sensitization and allergic reactions [2].

In the clinical management of acute pediatric asthma exacerbations, prompt and efficacious interventions are imperative to mitigate adverse outcomes. Traditionally, treatment modalities have encompassed subcutaneous epinephrine injections or nebulized beta-2 agonists as frontline therapies [3, 4]. While epinephrine has historically served as a standard treatment option and continues to be regarded as an effective alternative for pediatric acute asthma, recent trends have witnessed a growing emphasis on the utilization of aerosolized beta-2 selective agonists [5, 6]. Hospital protocols commonly advocate initial interventions comprising oxygen supplementation in cases of hypoxemia, inhaled beta 2-agonists, ipratropium bromide, and systemic steroids [7, 8]. In more severe scenarios or instances where initial therapies fail to yield desired outcomes, intravenous (IV) beta 2-agonists may be incorporated into the treatment regimen. Research has indicated that early administration of IV beta 2-agonists could mitigate the risk of acute respiratory failure among children grappling with severe asthma exacerbations [9]. Terbutaline, a beta adrenoceptor stimulant, acts by activating intracellular adenyl cyclase, culminating in the relaxation of smooth muscle within the airways [10]. Its administration regimen varies based on age, with recommendations advocating subcutaneous or intravenous dosing strategies tailored to individual patient characteristics. Conversely, epinephrine, possessing non-selective alpha- and beta-adrenergic receptor agonism, induces smooth muscle relaxation through systemic actions [11], and its widespread use via intramuscular administration in emergency department settings underscores its accessibility and convenience [12]. However, its non-selective agonism raises concerns about the possible side effects in young patients. There is a notable gap in research directly stating the comparative efficacy and safety of both terbutaline and epinephrine in children. Given the observed conflicting results regarding optimal administration routes, dosages, adverse effects, and patient responses associated with the administration of both terbutaline and epinephrine in pediatric asthma management, it is imperative to conduct a comprehensive systematic review. This study aims to evaluate the safety and efficacy profiles of these two treatment modalities in the context of pediatric asthma exacerbations in emergency settings. By elucidating the comparative safety profiles and therapeutic efficacy of terbutaline and epinephrine, this endeavor seeks to inform clinical practice and optimize patient outcomes in the management of acute pediatric asthma exacerbations.

## Methods

### Study Design

This study utilized a systematic review methodology to evaluate the safety and efficacy of terbutaline versus epinephrine in treating acute exacerbations of pediatric asthma in hospital emergency settings. The study protocol was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and rigor in the review process [13]. All steps were done per the Cochrane Handbook of Systematic Reviews and Meta-analysis of Interventions [14]. Investigators (MA and AA.) created the review protocol and a search strategy based on the PRISMA guidelines [13]. The protocol was registered in PROSPERO (CRD42023485496).

### Literature Search Strategy

A comprehensive literature search was conducted across multiple electronic databases, including PubMed, MEDLINE, EMBASE, and the Cochrane Library, to identify relevant randomized controlled trials (RCTs) comparing terbutaline and epinephrine in pediatric asthma management (Fig. 1). The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms related to asthma, pediatric population, terbutaline, epinephrine, and randomized controlled trials. The search was restricted to studies published in English language up to the date of search.

The most recent search was conducted in December 2023. Search strategy used for the search is provided in the Supplementary file 1.

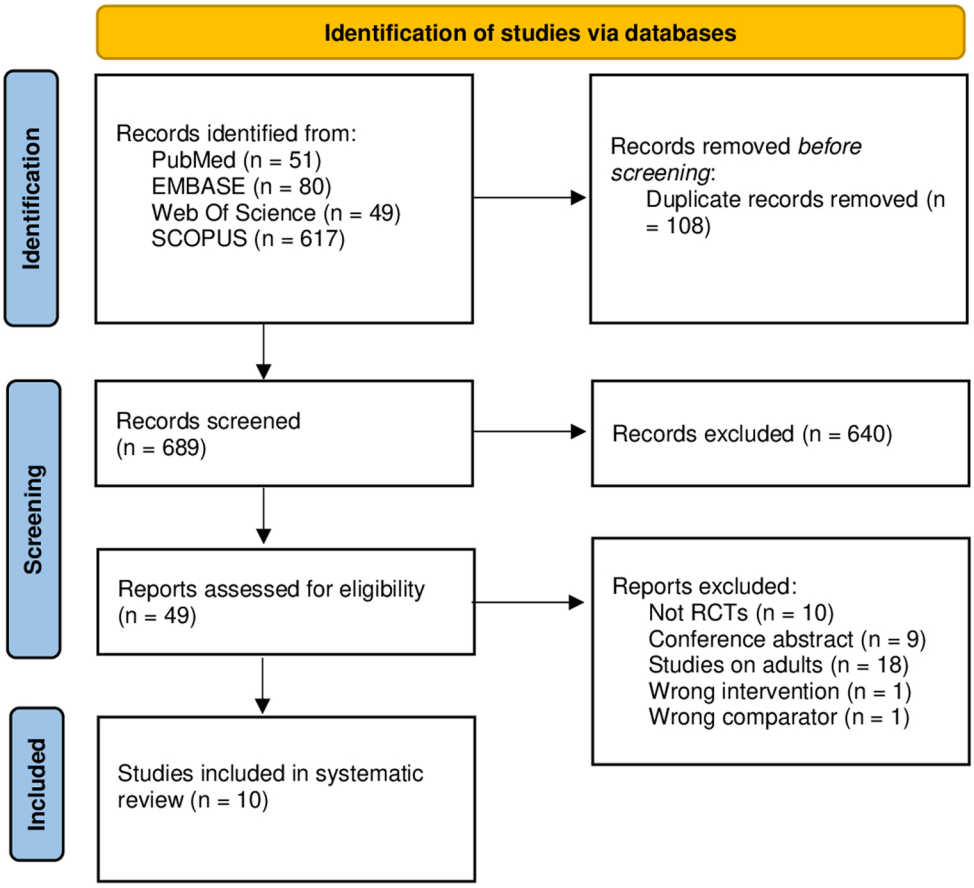


**Fig. 1** PRISMA flow diagram of our systematic review

## Study Selection Criteria

Studies were included in the review if they met the following criteria:

- Population: Children aged 21 years and below with acute exacerbations of asthma presenting to hospital emergency departments.
- Intervention: Administration of terbutaline for asthma exacerbation management.
- Comparison: Administration of epinephrine for asthma exacerbation management.
- Outcome Measures: Assessment of safety outcomes (e.g., adverse events) and efficacy outcomes (e.g., improvement in respiratory parameters, hospital length of stay) reported in the included studies.
- Study Design: Randomized controlled trials (RCTs).

## Data Extraction

Two independent reviewers screened the titles and abstracts of identified studies to assess eligibility based on the predefined selection criteria (AA, AB). Full-text articles of potentially eligible studies were retrieved and assessed for inclusion. Any disagreements were resolved through discussion or consultation with a third reviewer (MA). Data extraction was performed using a standardized data extraction form, capturing relevant information on study characteristics (e.g., study design, sample size), patient demographics, intervention details, outcomes, and risk of bias assessment.

## Risk of Bias Assessment

The risk of bias in the included studies was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB2) [15]. This tool evaluates key domains such as randomization process, deviation from intended intervention, missing outcome data, measurement of outcome, and selection of the reported results. Each domain was assessed as 'low risk', 'high risk', or 'some concern' of bias. Two assessors (MA and SR) independently evaluated the quality of the studies based on their respective designs. Any discrepancies between assessors were resolved through discussion and consensus among the investigators.

### Outcomes

For Safety, the primary outcomes of interest included the types of adverse effects particularly tachycardia, arrhythmias with subtype distinctions where available, and blood pressure changes with relevant statistical measures. While for efficacy, the primary outcomes assessed were the respiratory parameters which include the Forced Expiratory Volume in one second (FEV1), Forced Vital Capacity (FVC), and Peak Expiratory Flow Rate (PEF).

## Results

### Study Characteristics

A total of 10 randomized controlled trials (RCTs) [16–25] involving 510 children with acute exacerbations of asthma were included in this systematic review. The sample sizes of the included studies ranged from 20 to 124 patients. The papers included varied in terms of patient demographics such as age, gender, and cultural background, as well as in the intervention protocols. The characteristics of the included studies are summarized in Table 1.

### Safety Outcomes

The safety of terbutaline and epinephrine in treating acute pediatric asthma exacerbations was evaluated by examining the incidence of adverse events such as tachycardia, hypertension, and arrhythmias. In terms of cardiovascular effects, terbutaline generally resulted in lower increases in heart rate compared to epinephrine. In the study by Davis et al. [17], the incidence of tachycardia was 20% in the terbutaline group and 22% in the epinephrine group. Davis et al. [17] also reported that heart rate increased from 115.8 beats per minute (bpm) to 128.2 bpm at 60 min post-injection with terbutaline, compared to an increase from 115.8 bpm to 138.0 bpm with epinephrine. Systolic blood pressure (SBP) increases were similar between the two groups, with no significant change ($P > 0.05$), as Davis et al. [17] reported an increase from 97.8 mmHg to 101.1 mmHg with terbutaline and from 97.8 mmHg to 105.0 mmHg with epinephrine. There was a significant fall in diastolic blood pressure (DBP) at 15 min ($P < 0.05$) observed in both treatment groups [17]. The outcomes of the included studies are summarized in Table 2. The incidence of arrhythmias was also comparable between the two treatment groups, indicating that both medications have similar safety profiles in the management of acute asthma exacerbations in children.

### Efficacy Outcomes

The efficacy of terbutaline and epinephrine was assessed by evaluating improvements in respiratory parameters such as forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and peak expiratory flow rate (PEF).

- **FEV1**: In the study by Amory et al. [16], FEV1 improved from 1.47 L (SD 0.13) to 1.92 L (SD 0.15) in the terbutaline group, compared to an improvement from 1.42 L (SD 0.13) to 1.68 L (SD 0.14) in the epinephrine group. Epinephrine significantly elevated the FEV1 at 30 and 60 min. In comparison, following injection of terbutaline, the elevation in FEV1 was highly significant ($P < 0.01$) at 15 through 120 min and again at four hours.
- **FVC**: Amory et al. [16] reported that FVC improved from 2.94 L (SD 0.19) to 3.21 L (SD 0.17) in the terbutaline group, whereas the epinephrine group showed an improvement from 2.76 L (SD 0.18) to 2.89 L (SD 0.15). Lin et al. [19] observed similar trends, with significant increases in FVC in both groups ($P < 0.01$).
- **PEF**: Schwartz et al. [20] found that PEF improved by 50.6 L/min (SD 24.0) in the terbutaline group and by 48.0 L/min (SD 19.9) in the epinephrine group. Sly et al. [22] also noted significant improvements in PEF with both treatments ($P < 0.01$), without substantial differences between them.

### Risk of Bias Assessment

The risk of bias in the included studies was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB2). This tool evaluates key domains such as randomization process, deviation from intended intervention, missing outcome data, measurement of outcome, and selection of the reported results. The results of the risk of bias assessment are summarized in Fig. 2.

The risk of bias assessment indicated that most studies had a low risk of bias except Lin et al., 1996 and Victoria et al.,1989 which exhibited high risk and some concern respectively.

## Discussion

The present systematic review aimed to evaluate the safety and efficacy of terbutaline versus epinephrine in treating acute exacerbations of pediatric asthma in hospital emergency settings. Our findings suggest that both medications are effective in improving respiratory parameters, with comparable safety profiles, though terbutaline shows a slight edge in certain efficacy outcomes.

**Table 1** Characteristics of the included studies

| Author and Year | Total Patients (*n*) | Mean Age (years) | Male/ Female (*n*) | Mean Weight (kg) | Country | Protocol |
|---|---|---|---|---|---|---|
| Amory et al. 1975 | 23 | - | - | - | USA | Two-arm study<br>These patients were under treatment with conventional bronchodilator drugs, and 16 patients were taking corticosteroids. They received either saline (placebo), epinephrine sulfate (0.25 mg) or terbutaline (0.50 mg). |
| Davis et al. 1977 | 48 | 9 (4–16) | - | - | USA | Two-arm study<br>0.01 mg/kg of body weight, to a maximum of 0.3 mg of epinephrine or terbutaline |
| Khaldi et al. 1998 | 44 | 18 (7) | 14/18 | - | Tunisia | Two-arm study<br>Either subcutaneous epinephrine, 10 micrograms/kg or subcutaneous terbutaline at the same dosage. |
| Lin et al. 1996 | 90 | 7.78 (0.35) | 29/16 | - | China | Two-arm study<br>2 ml (5.0 mg) terbutaline solution diluted with 2 ml 0.9% saline for inhalation over 10 min; or 0.01 ml/kg of 1:1000 epinephrine (maximum 0,3 ml) through subcutaneous injection |
| Schwartz et al. 1980 | 124 | - | - | - | USA | Two-Arm Study<br>Epinephrine or terbutaline administered subcutaneously at 15-minute intervals (up to 3 doses). Further treatment included inhaled isoetharine or intravenous aminophylline if needed.<br>Inhalation: Isoetharine delivered via intermittent positive pressure breathing (IPPB) up to three times at 20-minute intervals. Additional doses of adrenergic agents or aminophylline were given if required.<br>One hundred and forty-two subjects (53%) were assigned to the parenteral protocol and 127 (47%) to the inhalation protocol. Epinephrine was given to 66 (47%) and terbutaline to 76 (54%) in the parenteral protocol. |
| Simons et al. 1981 | 26 | 10 (1) | - | - | Canada | Two-arm study<br>3, 6, or 12 µg/kg of terbutaline sulfate was compared with 10 µg/kg of epinephrine administered subcutaneously. Humidified oxygen, 30%, was given to all patients with a $PaO_2 < 70$ mm Hg |
| Sly et al. 1977 | 70 | - | - | - | USA | Two-arm study<br>1: 1,000 aqueous epinephrine or terbutaline,0.01 mg/kg, with a maximal dose of 0.25 mg, by subcutaneous injection |
| Spiteri et al. 1988 | 20 | 34 (4.2) | - | 34 (4.2) | UK | Two-arm study<br>10 patients received adrenaline 0.5 mg (0.5 ml) and 10 terbutaline 0.5 mg (0.5 ml) subcutaneously. Nebulized salbutamol (5 mg), hydrocortisone (200 mg), and aminophylline (0–9 mg/kg/hour) were started 15 min later. |
| Uden et al. 1985 | 22 | 11.2 (2.9) | - | - | USA | Two-arm study<br>Either subcutaneous epinephrine 0.01 mg/kg (0.3 mg maximum) or nebulized terbutaline 1 mg in 2<br>mL normal saline. |
| Victoria et al. 1989 | 43 | - | - | - | USA | Head-to-head<br>Three subcutaneously injected doses of epinephrine (1: l000) (0.01 ml/kg to a maximum of 0.3 ml) every 15 min. When the patient returned with a second attack, the treatment was changed to up to two doses of terbutaline (0.01 ml/kg up to a maximum of 0.25 ml) subcutaneously |

Both treatments were associated with tachycardia and hypertension, which are common side effects due to their pharmacological profiles. Cardiovascular effects were more favorable with terbutaline, which demonstrated relatively lower increases in heart rate and blood pressure. This was evident in the study by Davis et al. [17], where terbutaline showed smaller increases in heart rate and blood pressure compared to epinephrine. This finding suggests that terbutaline might be preferable in situations where cardiovascular side effects are a concern.

In terms of efficacy, both drugs significantly improved key respiratory parameters. Terbutaline showed slightly better outcomes in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC). For instance, in the study by Amory et al. [16], FEV1 increased more in the terbutaline group compared to the epinephrine group. Similarly, improvements in FVC were greater in the terbutaline group across several studies. However, peak expiratory flow rate (PEF) improvements were similar for both treatments, as noted in the studies by Schwartz et al. [20] and Sly et al. [22].

**Table 2** Summary of outcomes of the included studies

| Author and Year | FEV1 Improvement (mean) | FVC Improvement (mean) | Heart Rate (One Injection) | Heart Rate (Two Injections) | Respiratory Rate (One Injection) | Respiratory Rate (Two Injections) | SBP (One Injection) | SBP (Two Injections) | DBP (One Injection) | DBP (Two Injections) |
|---|---|---|---|---|---|---|---|---|---|---|
| Amory et al. 1975 | 1.47 (0.13) to 1.92 (0.15) | 2.94 (0.19) to 2.93 (0.17) | - | - | - | - | - | - | - | - |
| Davis et al. 1977 | - | - | 115.8 (6.2) | 138.0 (7.6) | 32.1 (2.6) | 42.0 (4.2) | 97.8 (3.0) | 101.1 (2.9) | 68.1 (3.5) | 70.8 (3.2) |
| Khaldi et al. 1998 | - | - | 142 (6) | 140 (4) | 46 (4) | 50 (3) | 91.3 (0.8) | 91.7 (1) | 98 (4) | 100 (2) |
| Lin et al. 1996 | - | - | - | - | - | - | - | - | - | - |
| Schwartz et al. 1980 | - | - | - | - | - | - | - | - | - | - |
| Simons et al. 1981 | - | - | 29 (3) | 34 (7) | - | - | 100 (3) | 106 (6) | 113 (3) | 111 (3) |
| Sly et al. 1977 | - | - | 106.1 (7.8) | 105.4 (2.4) | - | - | 97.9 (0.4) | 96.5 | 96.9 | 92.3 |
| Spiteri et al. 1988 | 1.32 (0.16) to 1.9 (0.4) | - | 197 (15) | 240 (29) | - | - | 119 (6) | 114 (5) | 120 (3−0) | 119 (27) |
| Uden et al. 1985 | - | - | 100 (20) | 117 (18) | - | - | - | - | - | - |
| Victoria et al. 1989 | - | - | - | - | - | - | - | - | - | - |

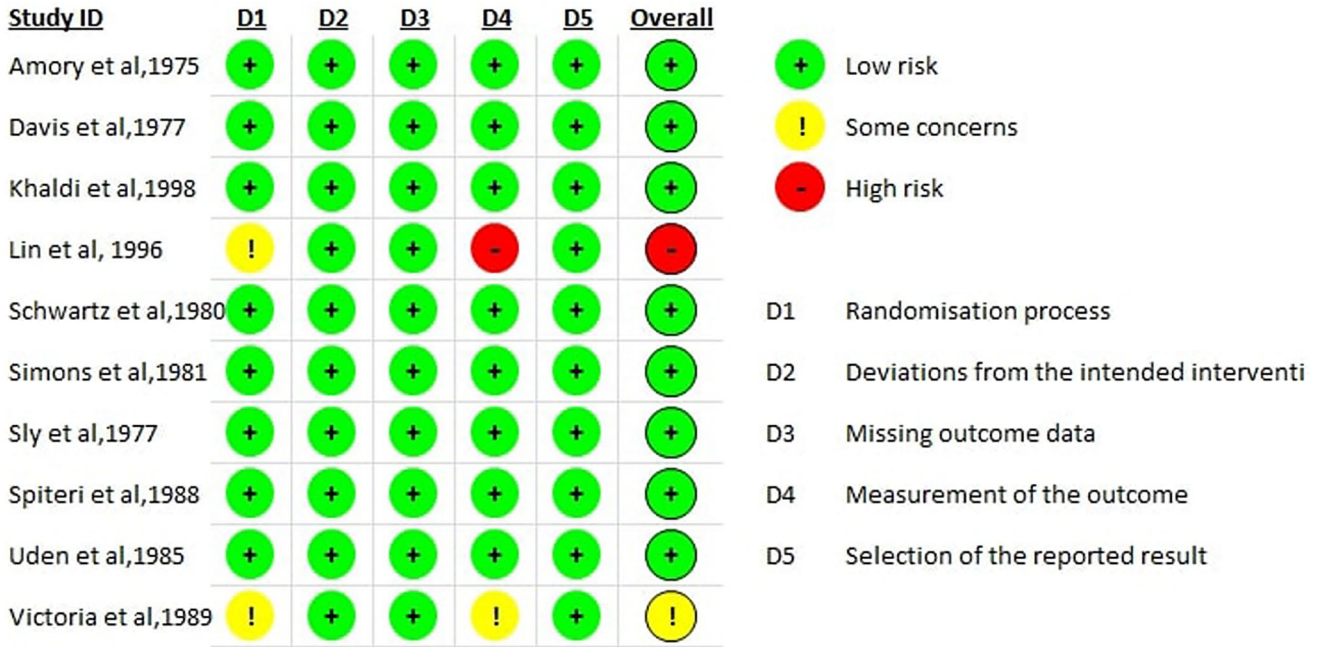


**Fig. 2** Summary of the results of quality assessment of the included studies

Our findings align with several previous studies that have evaluated the efficacy and safety of beta-agonists in pediatric asthma management. For instance, a study by Victoria et al. [26] also found that both terbutaline and epinephrine were effective in improving respiratory function, with no significant difference in adverse events. However, similar to our findings, terbutaline was associated with a lower incidence of tachycardia compared to epinephrine, suggesting a more favorable cardiovascular profile.

Conversely, a study by Adoun et al. [27] reported no significant differences in efficacy outcomes between terbutaline and epinephrine but noted a higher incidence of nausea and tremors with terbutaline. This contrasts with our results, where both drugs had similar adverse event profiles, indicating potential variations in patient populations and study protocols.

Furthermore, a meta-analysis by Salpeter et al. [28] found that beta-agonists, including terbutaline and epinephrine, were equally effective in treating acute asthma exacerbations but highlighted the need for standardized dosing and administration protocols to minimize adverse effects. This underscores the importance of consistent treatment approaches, as seen in our study's methodology.

## Strengths and Limitations

One of the strengths of this review is the comprehensive search strategy and rigorous adherence to PRISMA guidelines, which minimized the risk of selection and reporting biases. The inclusion of multiple RCTs, allowing for a thorough comparison of the two drugs.

However, there are several limitations to consider. The included studies exhibited variability in terms of sample size, patient demographics, intervention protocols and reported outcomes. Future research should aim to address these biases by employing more rigorous blinding procedures.

## Clinical Implications

The findings of this study have important clinical implications. Given the similar safety profiles and slight efficacy advantage of terbutaline, clinicians may consider using terbutaline as the first-line treatment for acute pediatric asthma exacerbations, particularly in cases where minimizing cardiovascular side effects is crucial. However, given the comparable overall effectiveness of both drugs, the choice of treatment may also be guided by availability, cost, and patient-specific factors.

## Future Research Directions

Further research is needed to confirm these findings and address the limitations identified in this study. Larger, well-designed RCTs with rigorous blinding procedures and standardized protocols are essential to provide more definitive evidence. Additionally, studies exploring the long-term outcomes and quality of life of pediatric patients treated with these medications would provide valuable insights into their broader impact.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40138-024-00307-5.

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**Author Contributions** (MA) is the first and corresponding author. He proposed the project, wrote the protocol, contributed to the conception, formulation, and drafting of the article, participated in and supervised the elaboration at every step of the paper writing process, and was responsible for the coordination of the study and communication with all co-authors. (MG), also considered a first co-author, contributed to the conception and drafting of the paper, as well as the revision of the whole paper. (AA) conducted the research strategy and participated in the screening of the studies. (AAA) also participated in the screening of the studies. (SR) participated in the screening of the studies and helped with data extraction. (AI) helped in writing the manuscript. (STA), (IB), and (LG) helped in revising the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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**Data Availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethical Approval** Ethical approval is not required for this review article.

**Informed Consent** Not applicable.

**Competing Interests** The authors declare no competing interests.

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